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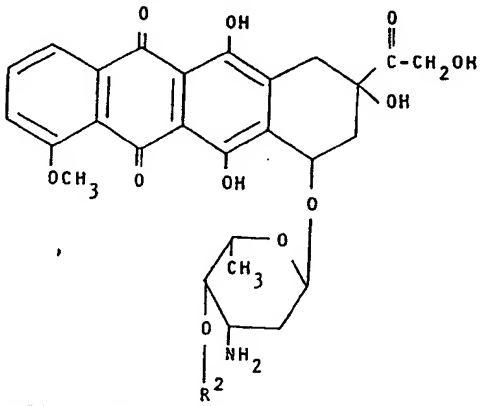
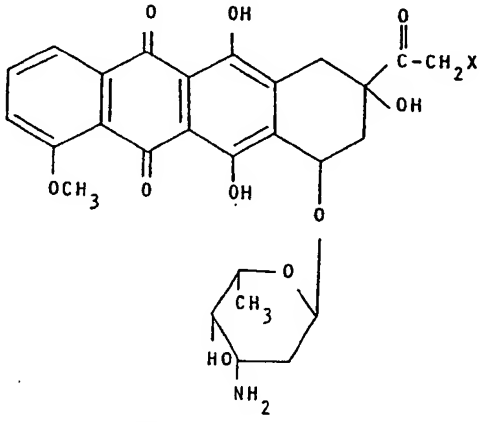
(54) **A new method for preparation of anthracycline derivatives.**

(57) An improved process for the production of anthracycline derivatives of the general formula;



wherein R^2 is hydrogen, tetrahydropyranyl, 6-acetoxymethyltetrahydropyranyl, 6-methoxytetrahydropyranyl, 6-carbomethoxytetrahydropyranyl, tetrahydrofuranyl, 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy) ethyl or cyclohexyloxyethyl group, which comprises reacting 14-halogenodaunomycin of the formula;



wherein X is halogen atom; or a salt thereof, with dihydropyrane, 2-acetoxymethyl-3,4-dihydro-2H-pyrane, 2-methoxy-3,4-dihydro-2H-pyrane, 2-carbomethoxy-3, 4-dihydro-2H-pyrane, dihydrofurane, methylvinylether,

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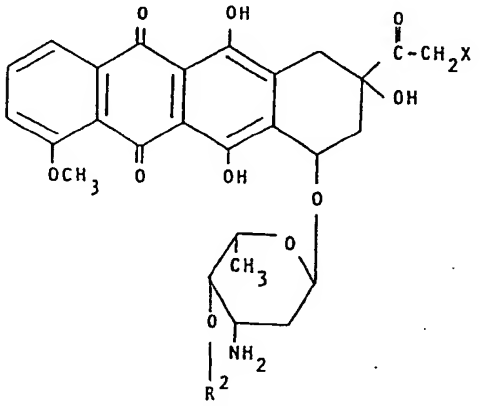
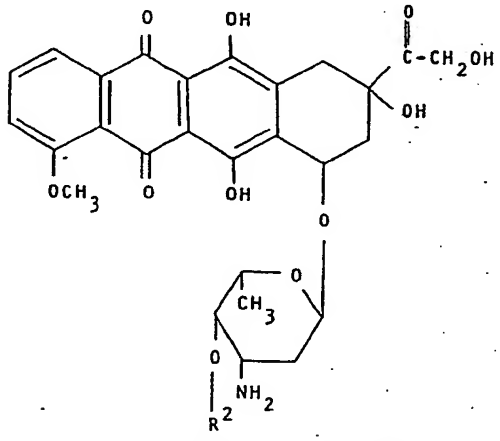
ethylvinylether, butylvinylether, isobutylvinylether, 6-methylheptylvinylether, cyclohexylvinylether, in the presence of an acid catalyst in an organic solvent, hereby obtaining 14-halogenodaunomycin derivatives of the formula;



wherein R^2, X have the same meaning as defined above except for hydrogen,
and treating with an alkali 14-halogenodaunomycin or the 14-halogenodaunomycin derivatives obtained in the preceding step, in a lower alcohol or aqueous acetone to effect hydrolysis, hereby obtaining anthracycline glycosides of the formula;



wherein R^2 has the same meaning as defined above, or an acid salt thereof.

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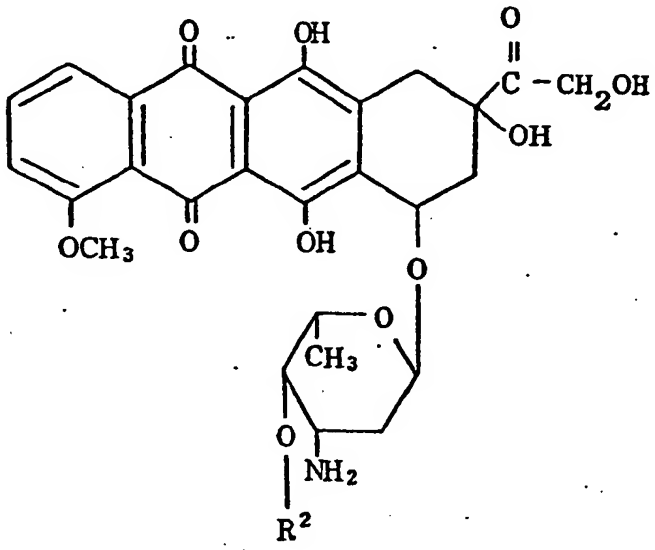
A new method for preparation of anthracycline derivatives

Detailed description of the invention

This invention relates to an improved process for the production by way of fewer steps of a less toxic, antitumor compounds, anthracycline glycosides of the general formula;

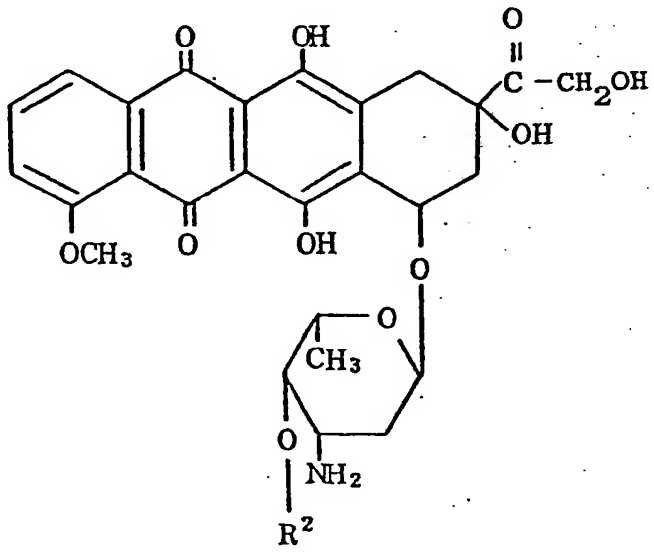


wherein R^2 is hydrogen, tetrahydropyranyl, 6-acetoxymethyltetrahydropyranyl, 6-methoxytetrahydropyranyl, 6-carbomethoxytetrahydropyranyl, tetrahydrofuranyl, 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl or cyclohexyloxyethyl group;

or an acid addition salt thereof.

This process consists of three steps; (1) halogenation of C-14 position of daunomycin with halogen in an inert organic solvent containing a less quantity of methanol (2) reacting the obtained 14-halogenodaunomycin, after treating with acetone, with dihydropyrane, dihydropyrane derivatives, alkylvinylether etc., to obtain C-4' position etherificated derivatives and (3) alkali hydrolysis of 14-bromodaunomycin or the etherificated derivatives obtained in the preceding step, in an organic solvent.

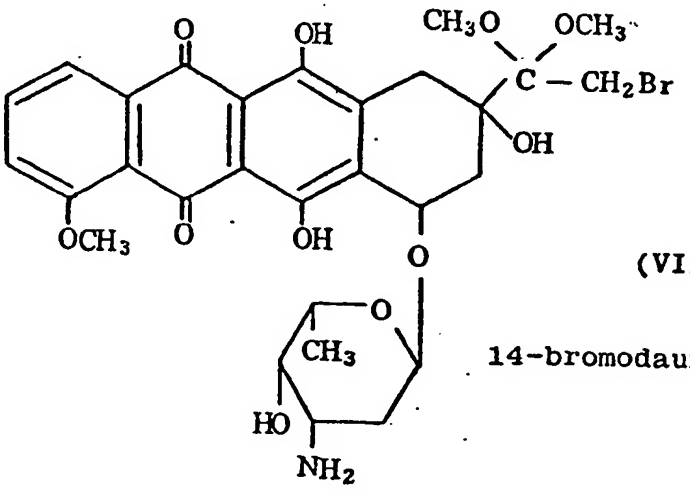
The present inventors have found that anthracycline glycosides of the formula (III);



(III)

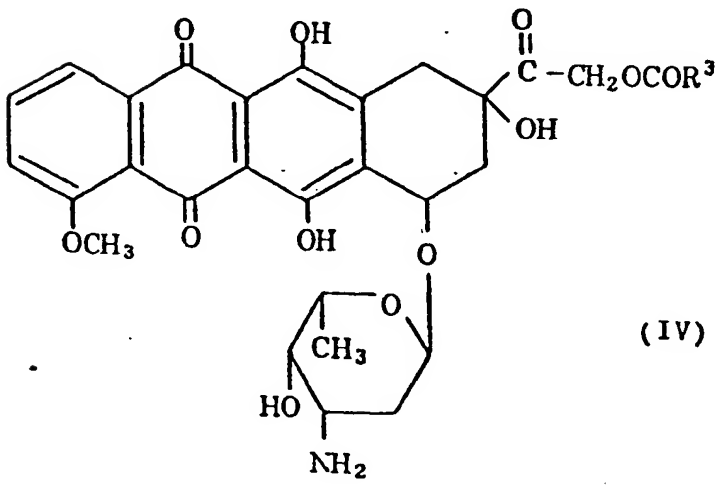
wherein R^2 is tetrahydropyranyl, 6-acetoxymethyltetrahydropyranyl, 6-methoxytetrahydropyranyl, 6-carbomethoxytetrahydropyranyl, tetrahydrofuranyl, 1-methoxyethyl,

1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl or cyclohexyloxyethyl group, have an effective antitumor activity, and that the anthracycline glycosides can be synthesized through 4 steps from the starting material, daunomycin that is ; (1) bromination of daunomycin with bromine to obtain the C-14 position brominated daunomycin derivatives of the formula (VII) (2) reacting said C-14 position brominated daunomycin with a compound of R^3 COOK, for example, in acetone, wherein R^3 is a C_1-C_6 alkyl group or benzyl group, K is an alkali metal to obtain a compound of the formula (IV)



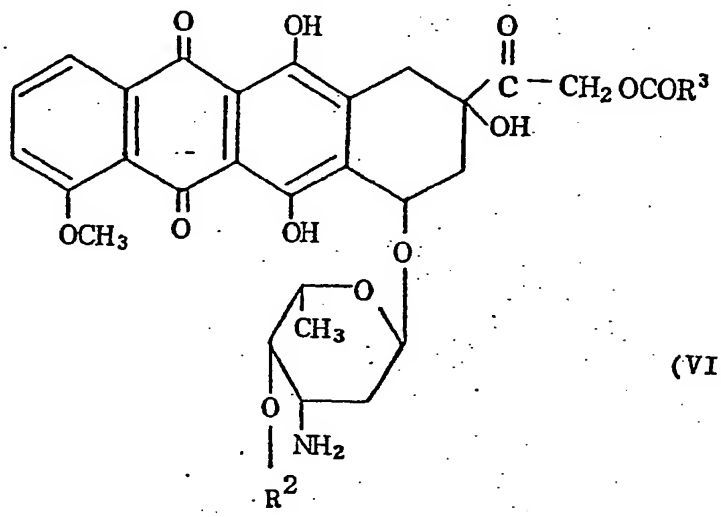
(VII)

14-bromodaunomycindimethylketal



(IV)

wherein R^3 has same meaning as defined above, (3) reacting the resulting compound (IV) with a dihydrofurane derivatives, dihydropyrane, a dihydropyrane derivatives or a vinylether derivatives etc., to obtain C-4' position substituted derivatives of the formula (VI);



(VI)

wherein R^2, R^3 have the same meaning as defined above and (4) hydrolysis of the resulting compound (VI) with an alkali in a lower alcohol or aqueous acetone to obtain C-14 position desacylated product of the formula (III). (see; Japanese patent application No. 11702/1979, No. 110255 and U.S. patent application serial No. 117163)

It has been found that when daunomycin is brominated according to this prior art process, there are obtained a compound of the formula (VII) mentioned above and a compound of the formula (I) as shown below simultaneously.

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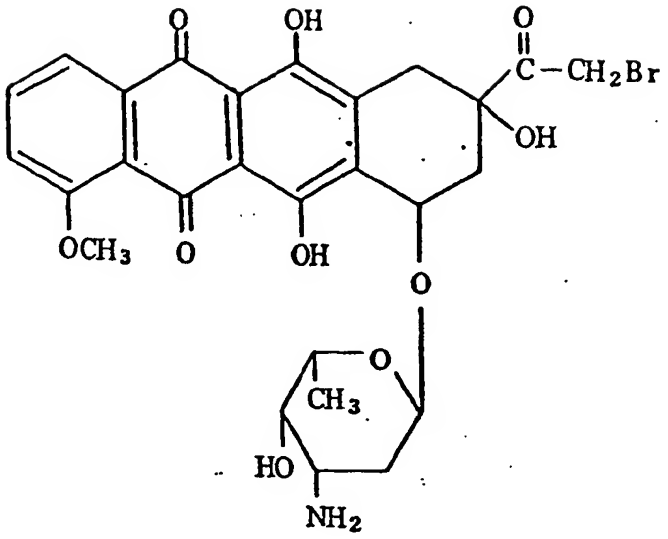
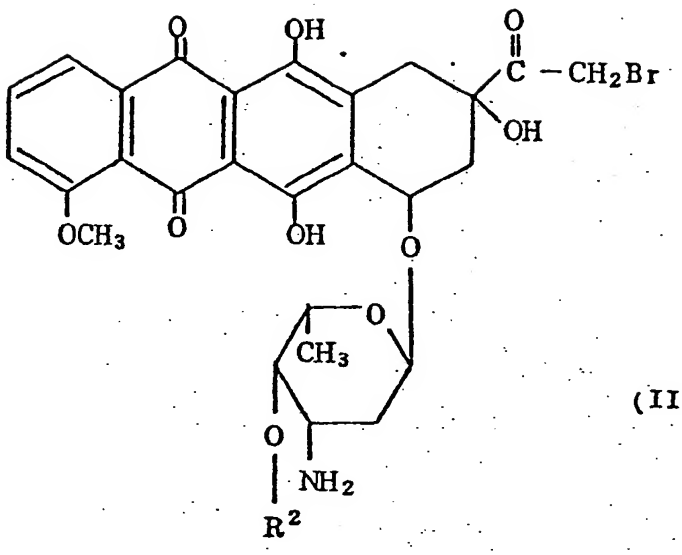


(I)

This fact was considered to result in a low yield of the final product (III), because it is synthesized using a mixture of compound (I) and (VII) as the starting material.

The present inventors have further made research on the production method to improve the yield of the final product (III), in the process of this research, it was found that C-14 position bromination of daunomycin using a less quantity of methanol than in said prior art process decreases the yield of (VII) and has the compound (I) obtained as main product.

The present inventors have also found that the compound (VII) which is now by-product is easily converted into the compound (I) by acetone treatment, and the crude product enriched in the compound (I) is converted with a hydroxyl reagent into a compound of the formula (II);



(II)

wherein R^2 is tetrahydropyranyl, 6-acetoxymethyltetrahydropyranyl, 6-methoxytetrahydropyranyl, 6-carbomethoxytetrahydropyranyl, tetrahydrofuranyl, 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl or cyclohexyloxyethyl group,

by treating it with dihydropyrane, 2-acetoxymethyl-3,4-dihydro-2H-pyrane, 2-methoxy-3,4-dihydro-2H-pyrane, 2-carbomethoxy-3,4-dihydro-2H-pyrane, dihydrofurane, methylvinylether, ethylvinylether, butylvinylether, isobutylvinylether, 6-methylheptylvinylether or cyclohexylvinylether, in higher yield, which is easily hydrolyzed by treating with an alkali in an lower alcohol or aqueous acetone to obtain the final

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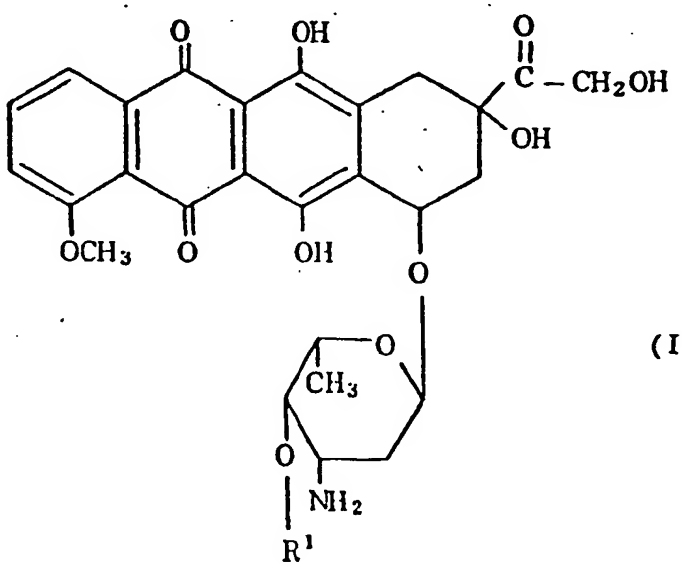
product (III), whereas ketal bromide compounds obtained from compounds (VII) are not easily hydrolyzed into hydroxyl compounds of the formula (III) by the same treatment.

Therefore, this invention relates to a production method of the final product (III) from the starting material, daunomycin in a higher yield (above 16 %), by way of 3 steps without the step of C-14 acylation with R^3COOK as in the prior art process.

This invention, in its scope, comprises the production process of adriamycin from daunomycin which does not need the etherification of C-4' position of 14-bromodaunomycin.

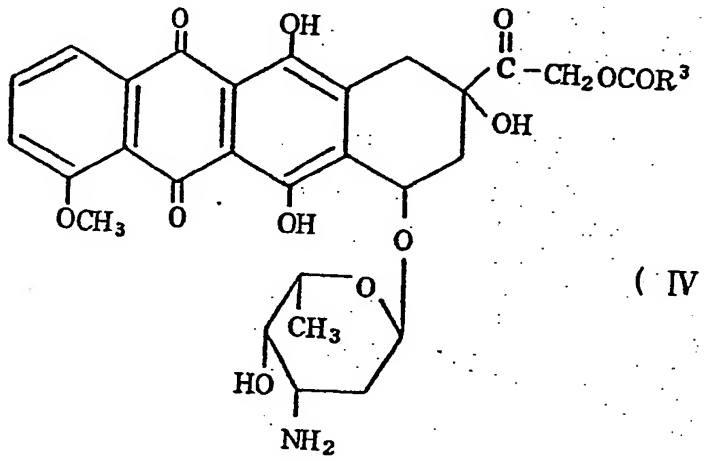
The present invention relates to a new method for preparation of anthracycline derivatives. More particularly, it relates to a novel method for preparation from daunomycin of anthracycline glycosides represented by the following formula (III) or their acid addition salts



(III)

where R^1 is selected from the group consisting of tetrahydropyranyl; 6-substituted tetrahydropyranyl such as 6-acetoxymethyltetrahydropyranyl, 6-methoxy-tetrahydropyranyl and 6-carbomethoxytetrahydropyranyl; tetrahydrofuranyl; alkyloxyethyl such as 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl and cyclohexyloxyethyl; and hydrogen.

The present inventors have succeeded in synthesis of new, less toxic anthracycline glycosides with antitumor activity by treating daunomycin derivatives represented by formula (IV)



(IV)

where R^3 is an alkyl group having 1 - 6 carbon atoms or benzyl,

with a hydroxyl reagent such as dihydropyrane, its derivatives, dihydrofurane derivatives and vinyl ether derivatives in order to incorporate at C-4' position a tetrahydropyranyl, 6-substituted tetrahydropyranyl, tetrahydrofuranyl, or 1-

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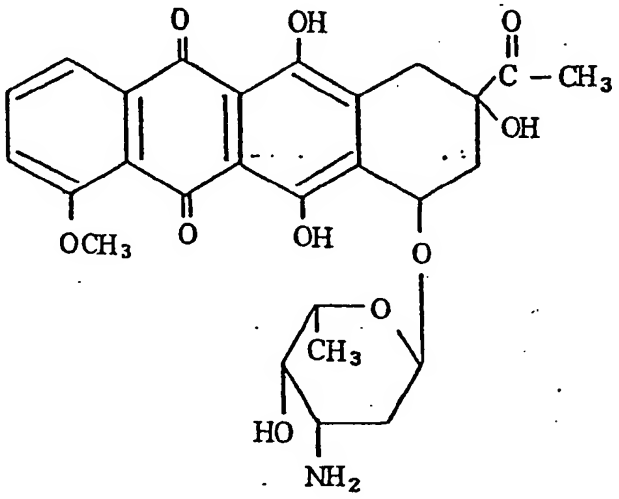
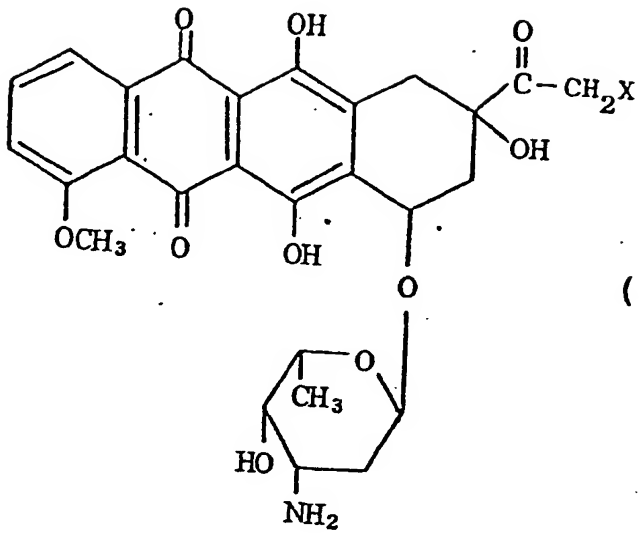
alkoxyethyl group removing an acyl group at C-14 position from the product by hydrolysis, Based on these findings, a patent application was filed (Japanese Patent Application No. SHO 54-110255. U.S. Patent Application No. 117163). In summary, daunomycin represented by formula (V)

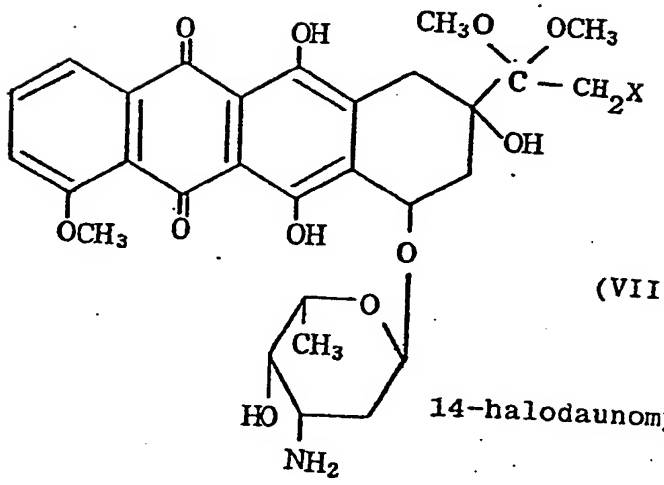


(V)

or its salts are halogenated, and preferably brominated, at C-14 position in the presence of an inert organic solvent to provide halogenated preferably brominated daunomycin which has been proved to be a mixture of two types of compounds of formula (I) and formula (VII) as shown below.



(I)



(VII)

14-halodaunomycindimethylketal

where X is a halogen atom;

or its salts. The halogenated, preferably brominated daunomycin is converted to the aforementioned compound represented by formula (IV), for example, by treating with R^3COOK (where R^3 is an alkyl group having 1 - 8 carbon atoms or benzyl; and K is an alkaline metal atom) in acetone. The ester represented by formula (IV) is

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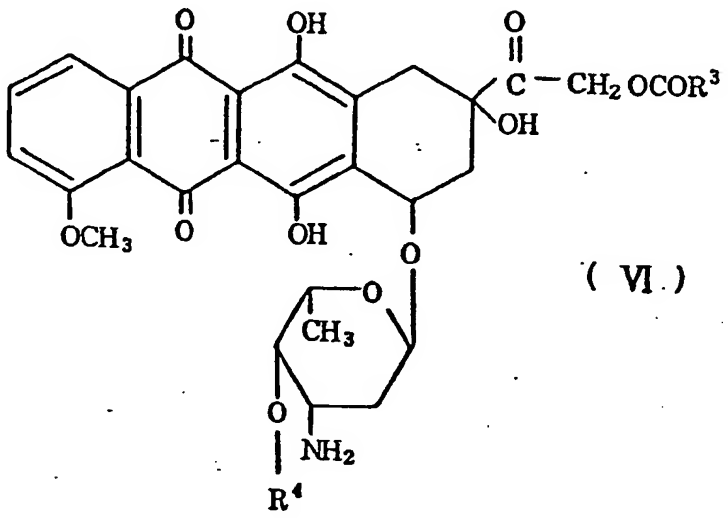
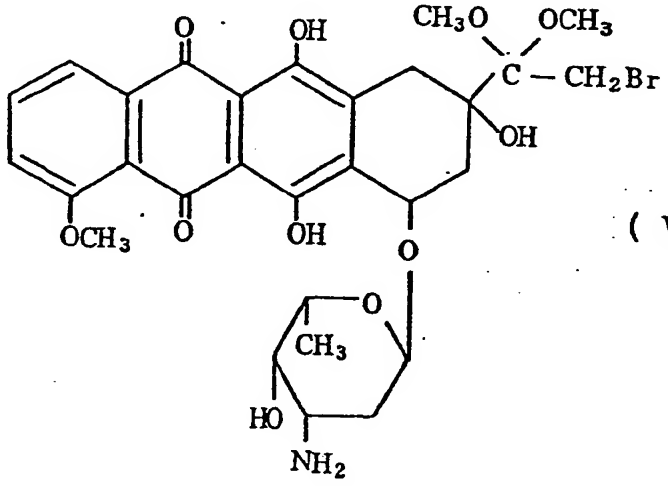
allowed to react with dihydrofurane derivatives, dihydropyrane, dihydropyrane derivatives and vinyl ether derivatives such as alkylvinyl ether in the presence of an acid catalyst such as p-toluenesulfonic acid in dimethylformamide to yield an intermediate compound represented by formula (VI)



(VI)

where R^3 has tne same definition as for formula (IV); and R^4 is selected from the group consisting of 1-alkoxyethyl such as 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl; tetrahydrofuranyl; tetrahydropyranyl, and 6-substituted tetrahydropyranyl such as 6-methoxytetrahydropyranyl, 6-carbomethoxytetrahydropyranyl and 6-acetoxymethyltetrahydropyranyl.

The final product represented by formula (III) is obtained from the intermediate compound of formula (VI) by hydrolytic desacylation at C-14 position with alkali in an organic solvent such as lower alcohol and aqueous acetone. In other words, starting from daunomycin, the final 4'-substituted derivatives of the formula (III) are obtained by four steps of treatment in the above patent application (hereinafter referred to as prior art process). Thus this method of preparation has some disadvantages in complicated process and low yield of reaction. A possible reason for low yield of reaction might be found in the observation that, on bromination of daunomycin at C-14 position, a by-product represented by formula (VII)



(VII)

is formed in addition to the aimed compound represented by formula (I), resulting in the poor yield of the latter

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keto type compound. Moreover the complicated process consisting of 4 steps of reaction seems to be reflected in the overall low yield. Under these circumstances, a more reasonable method of preparation has been sought for.

Therefore, the present inventors have made research on improved method in order to raise the yield of the final product of the formula (III), in the course of this research, they have found a very interesting fact that C-14 position bromination of daunomycin using a less quantity of methanol than in said prior art process decreases the yield of the compound (VII) and produces the keto compound (I) as main product.

The present inventors have also found a fact that the treatment with acetone at room temperature transforms the compound of the formula (VII) which is now by-product to the keto compound represented by formula (I) and the material enriched in said compound of the formula (I) is converted effectively into a compound of the formula (II) by treatment with a hydroxyl reagent.

In practice, as detailed later in Examples, a daunomycin acid addition salt such as daunomycin hydrochloride in dry methanol is brominated with bromine in methylene chloride in the presence of methyl orthoformate or dioxane and then the reaction mixture is poured in dry ether. The treatment of the resulting precipitates with acetone gives the compound represented by formula (I).

In the present invention the aimed compounds, new adria-

mycin derivatives represented by formula (III), are obtained by hydrolyzing the compound represented by formula (I) that can be derived from daunomycin in a good yield (needless to say, the compound represented by formula (II) per se is also advantageously employable as the starting material); or by converting the compound represented by formula (I) to the 4'-substituted derivatives represented by formula (II) which have a tetrahydropyranyl, 6-substituted tetrahydropyranyl, tetrahydrofuranyl or 1-alkoxyethyl group at C-4' position followed nydrolysis of the 4-substituted derivatives represented by formula (II) to the final product of the formula (III)

In other words, the aforementioned prior art process is characterized by 4 steps of treatment consisting of bromination at C-14 position; substitution of the bromine with an acyloxy group for protection; pyranylation, furanylation or etherification at C-4' position; and deacylation at C-14 position. In contrast, according to the method of the present invention, the aimed compounds represented by formula (III) can be prepared in a higher yield by 3 steps of treatment from daunomycin in which daunomycin is brominated at C-14 position in a less quantity of methanol to give largely the keto type of 14-bromodaunomycin of the formula (I) and then, without substitution of the bromine with an acyloxy group, is pyranylated,. furanylated or etherified before debromination.

In summary, according to the present invention, the

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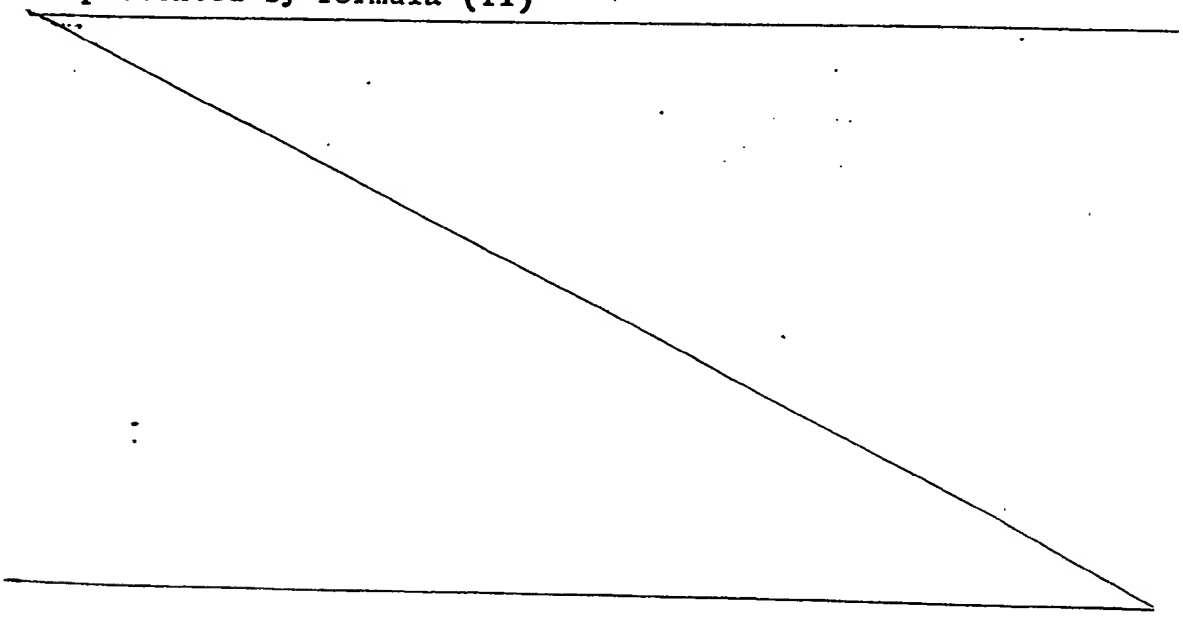
production process of the final product (III) from daunomycin consists of three steps;

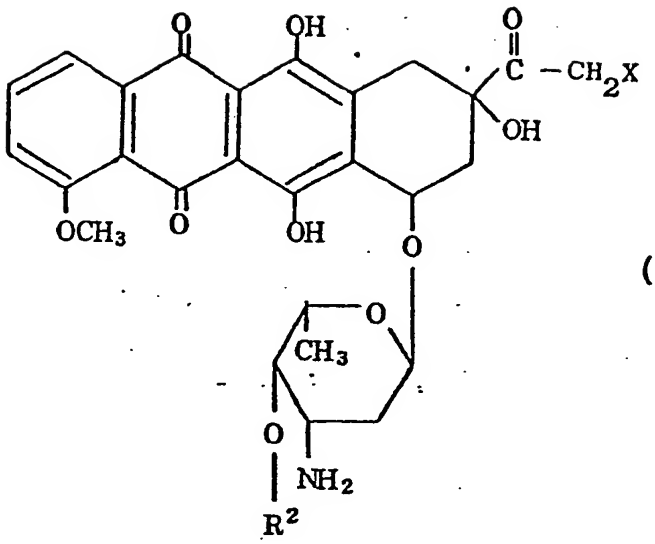
(1) halogenation (preferably bromination) at C-14 position of daunomycin of the formula (V) with halogen (preferably bromine) in an inert organic solvent containing a less quantity of methanol

(2) reacting the obtained halogenated (preferably brominated) daunomycin pretreated with acetone, with a hydroxyl reagent, to effect pyranylation, furanylation, etherification at C-4' position,

(3) hydrolysis of halogenated daunomycin derivatives obtained in (II) in an organic solvent.

The compound represented by formula (I) is treated with dihydropyrane, dihydrofurane, their derivatives or alkyl-vinyl ether in the presence of an acid catalyst such as sulfonates (for example, p-toluenesulfonate and camphor-sulfonate) in an inert organic solvent such as dimethyl-formamide to provide the 4'-substituted derivatives represented by formula (II)





(II)

where R^2 is selected from the group consisting of tetrahydropyranyl; 6-substituted tetrahydropyranyl such as 6-acetoxymethyltetrahydropyranyl, 6-methoxytetrahydropyranyl and 6-carbomethoxytetrahydropyranyl; tetrahydrofuranyl, and alkyloxyethyl such as 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl and cyclohexyloxyethyl; X is a halogen atom,

and the 4'-substituted derivatives represented by formula (II) are debrominated with alkali at position 14 in aqueous acetone or in a lower alcohol.

It is apparent that the method of the present invention is

industrially more advantageous than prior art process, because the ketal-type of the halogenation product is least formed and the one step-less process results in the improved yield and purity of the aimed products.

It can also easily be understood that the method of the present invention is profitable for efficient synthesis of adriamycin from daunomycin without the above-described 4'-substitution step.

As the typical 4'-substitutes, tetrahydropyranyl and tetrahydrofuranyl are described in the attached examples. As detailed in the aforementioned patent application, dihydropyrane compound, dihydrofurane compound and alkylvinyl ether compounds providing 6-substituted tetrahydropyranyl such as 6-methoxytetrahydropyranyl, 6-carbomethoxytetrahydropyranyl and 6-acetoxytetrahydropyranyl; tetrahydrofuranyl and alkyloxyethyl such as 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl and cyclohexyloxyethyl are also desirably employed for 4'-substitution.

For tetrahydropyranylation, tetrahydrofuranylation and etherification (these can collectively be called etherification in a broad sense), benzene, toluene, dimethylformamide(DMF), tetrahydrofurane(THF), dimethylsulfoxide(DMSO), dioxane and acetonitrile are used as anhydrous solvent solely or in mixture. As the acid catalyst, sulfonates and particularly aromatic sulfonates such as p-toluenesulfonate, benzenesulfonate

and DL-camphorsulfonate are preferable. It is needless to say, of course, that other common acid catalysts are also employable in the present invention. Favorable combinations of the acid catalysts with the solvents are p-toluenesulfonate in anhydrous DMF, p-toluenesulfonate in a mixture of anhydrous DMSO and anhydrous THF or in a mixture of anhydrous DMSO and anhydrous dioxane, and DL-camphorsulfonate in anhydrous DMF. The etherification step can usually be completed in 20 minutes - 50 hours at room temperature.

Hydrolysis of 14-bromodaunomycin derivatives in a water-miscible solvent such as lower alcohol (for example methanol and ethanol) and aqueous acetone is carried out at room or slightly elevated temperature with alkali such as aqueous sodium hydroxide, while the extent of debromination is monitored by thin layer chromatography.

The products of the present invention are obtained in the free base form or the acid addition salt form depending on the starting material employed. If desired, the free base can be converted to the acid addition salt by usual methods of salt formation or the acid addition salt can be recovered in the free base form.

The tetrahydropyranyl, tetrahydrofuranyl or alkoxyethyl derivatives obtained by the etherification method of the present invention are a diastereomic mixture of isomers a and b. Thus they are separated into individual isomers and purified at room temperature by conventional methods

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of purification for anthracycline glycosides.

For example, after solid matters are removed by filtration, the filtrate containing the aimed products is concentrated to dryness to give crude powder. The crude powder is then subjected to purification by alumina or silica gel column chromatography, thin layer chromatography and the like. The diastereomers a and b of the 4'-O-substituted derivatives of the present invention seem to have absolute configurations R and S at the chiral center, because the two isomers differ in the chemical shift of the methine protons corresponding to the chiral center.

The final compound of the formula (III) according to this invention process are obtained in the yield based on daunomycin as shown in the Table 1.

Some examples of the present invention are described hereinafter but they should not be construed to limit the scope of invention in any way.

Example 1. 4'-O-Tetrahydropyranyladriamycins a and b

14-Bromodaunomycin hydrochloride (6.0 g) is dissolved in 100 ml of anhydrous dimethylformamide. To this solution, 25 ml of dihydropyrane and 25 mg of DL-camphorsulfonic acid are added and allowed to react at 25°C for 6 hours. Monitoring by silica gel thin layer chromatography (chloroform : methanol = 9 : 1 by volume) reveals the formation of two new compounds having Rf values of 0.32 and 0.44 with the concomitant disappearance of the starting material. The reaction mixture is poured in a

mixture of 1 liter acetone and 500 ml water and is kept at pH 11±0.1 under vigorous agitation with 0.5N trisodium phosphate. The two compounds having the said Rf values are found to change slowly to new products having Rf values of 0.12 and 0.23 by thin layer chromatography. After reaction for one hour at 25°C, the solution is neutralized by 1N hydrochloric acid and acetone is removed by evaporation under reduced pressure. The concentrate is extracted with 500 ml and 200 ml of methylene chloride. The methylene chloride extracts are combined; rinsed three times with 500 ml of water; and then dried over anhydrous sodium sulfate. The methylene chloride solution is charged on a column of 50 g silica gel (E. Merck, Darmstadt; Kieselgel 60, 70 - 230 mesh) and the column is washed with 1 liter of chloroform. Chloroform-methanol mixture is used for elution. Each 20 ml fraction is monitored by thin layer chromatography for product analysis. Fractions containing a product of Rf 0.23 are combined and concentrated under reduced pressure to provide 1.7 g of dark red solid matters of 4'-O-tetrahydropyranyladriamycin b (yield 29 %). Recrystallization from methylene chloride gives 0.54 g of the above product in the pure state. Melting point under decomposition : 191 - 192°C.

NMR($CDCl_3$, ppm) 1.33(6'-H), 1.50 ~ 1.96(tetrahydropyranyl-H), 4.07(4'-O-methyl-H), 4.73(14-H), 4.72(anomeric H of the tetrahydropyranyl group), 5.27(1'-H), 7.31 ~ 8.06 (1 ~ 3-H)

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IR(KBr, cm^{-1}) 3680, 3530, 3390, 1720, 1618, 1578, 1407, 1294, 1209, 1121, 1110, 1075, 1000, 988, 960, 815, 761.

$[\alpha]_D^{19}$ + 202.7° (c=0.75, $CHCl_3$)

Fractions containing the product with Rf 0.13 give 0.65 g of 4'-O-tetrahydropyranyladriamycin a.

Example 2. 4'-O-Tetrahydropyranyladriamycins a and b.

Daunomycin hydrochloride (226 mg) is dissolved in 4 ml of anhydrous methanol and is mixed with 0.2 ml of methyl orthoformate and 8 ml of dioxane. After 0.83 ml of bromine solution in methylene chloride (10 % w/v) is added, the reaction is carried out at 25°C for 40 minutes. The reaction mixture is poured in 50 ml of dry ether and the precipitates formed are recovered by centrifugation. The supernatant solution is discarded. After washing twice with 5 ml of dry ether, the precipitates are treated under agitation in 12 ml of acetone at 25°C for one hour. The treated deposits are collected by centrifugation; rinsed twice with ether and dried to give 226 mg of red powder of 14-bromodaunomycin hydrochloride(yield 87 %). The red powder is dissolved in 7 ml of dry dimethyl-formamide and mixed with 2 ml of dihydropyrane and 10 mg of p-toluenesulfonic anhydride. After reaction at 20°C for 3 hours, the reaction mixture is poured in a mixture of 60 ml acetone and 30 ml water and allowed to stand for 30 minutes at pH 11.0 - 11.5 under control with 1N sodium hydroxide. The solution is neutralized with diluted

hydrochloric acid and most of the acetone is evaporated off under reduced pressure. The concentrate is extracted three times with 30 ml of chloroform. The chloroform extracts are combined; rinsed three times with water and dried over anhydrous sodium sulfate. The chloroform solution is concentrated under reduced pressure to give dark red solid matters. Purification is performed with silica gel thin layer plates (E. Merck, Darmstadt; silica gel 60, 20 x 20 cm, 2mm thick). Satisfactory separation is obtained by developing with a solvent mixture of chloroform and methanol (9 : 1). Silica gel powder corresponding to the area of Rf 0.23 is scraped off and eluted with a mixture of chloroform and methanol (2 : 1). The eluate is concentrated to dryness under reduced pressure to provide 54 mg of reddish brown solid of 4'-O-tetrahydropyranyladriamycin b (overall yield 21 %).

Similarly 39 mg of 4'-O-tetrahydropyranyladriamycin a (overall yield 16 %) is recovered from the area of Rf 0.13.

Example 3. 4'-O-Tetrahydrofuranyladriamycin.

14-Bromodaunomycin hydrochloride (1.10 g) in 30 ml of dry dimethylformamide is mixed with 0.2 ml of dihydrofurane and a small amount of DL-camphorsulfonic acid and then allowed to react at a temperature of 20 - 25°C for 3 hours. The reaction solution is diluted with a mixture of 200 ml acetone and 100 ml water and stirred vigorously for one hour while the pH of the solution is maintained at

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11 ± 0.1 by addition of 0.5 N trisodium phosphate. After neutralization with 1 N hydrochloric acid, the acetone is removed by evaporation in vacuo. The concentrate is submitted to extraction twice with 50 ml of methylene chloride and the methylene chloride extracts are combined and rinsed three times with water. The methylene chloride solution is passed through a column of 20 g silica gel (E. Merck, Darmstadt; Silica gel 60) and the adsorbed products are separatedly eluted with a solvent system of chloroform and methanol under monitoring by thin layer chromatography (chloroform ; methanol = 9 : 1 by volume). Fractions containing compounds of Rf 0.16 and 0.19 are collected and concentrated to dryness to give 350 mg of dark red solid of 4'-O-tetrahydrofuranyladriamycin (yield 33 %).

Melting point under decomposition : 189 - 194°C.

NMR($CDCl_3$, ppm) 1.25 ~ 1.27(6'-methyl-H), 1.67 ~ 2.30 (tetrahydrofuranyl-H), 4.07(4-O-methyl-H), 4.75(14-H), 5.17 and 5.38(anomeric H of the tetrahydrofuranyl group), 5.30(1'-H), 7.30 ~ 8.07(1 ~ 3-H).

Example 4. Adriamycin hydrochloride.

To a solution of 226 mg of daunomycin hydrochloride in 4 ml of anhydrous methanol, 0.2 ml of methyl orthoformate and 8 ml of dioxane are added. After 0.83 ml of bromine-methylene chloride solution (10 %, w/v) is poured therein, the reaction is carried out at 25°C for 40 minutes. The reaction solution is diluted with 50 ml of dry ether and

the formed precipitates are collected by centrifugation, whereas the supernatant is discarded. The precipitates are washed twice with 5 ml of dry ether and then treated under agitation with 12 ml of acetone at 25°C for one hour. After dilution with aqueous acetone, the acetone solution is kept for 20 minutes at pH 11 ± 0.1 by adjusting with 0.5 M sodium phosphate. The treated solution is neutralized and the acetone is evaporated off in vacuo. The product is extracted repeatedly with a chloroform-methanol mixture and the extracts are combined and dried over anhydrous sodium sulfate.

After concentration in vacuo, adriamycin hydrochloride is forced to precipitate by adding methanolic hydrochloric acid and anhydrous ether to the chloroform concentrate.

Melting point under decomposition : 204 ~ 205°C.

$[\alpha]_D^{20}$ +248° (c=0.1, CH_3OH)

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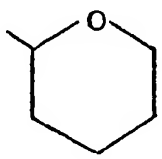
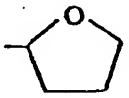
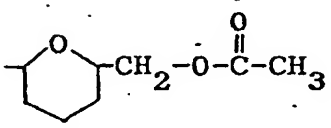
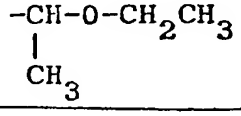
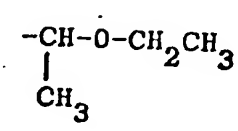
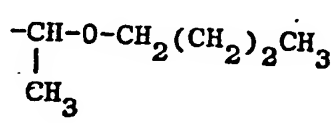
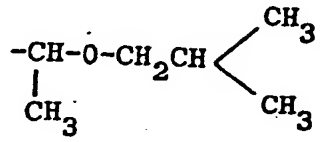
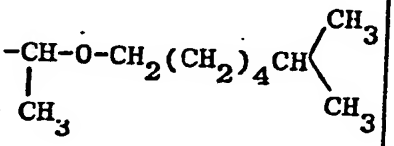
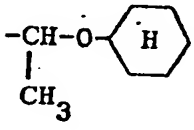
Table 1

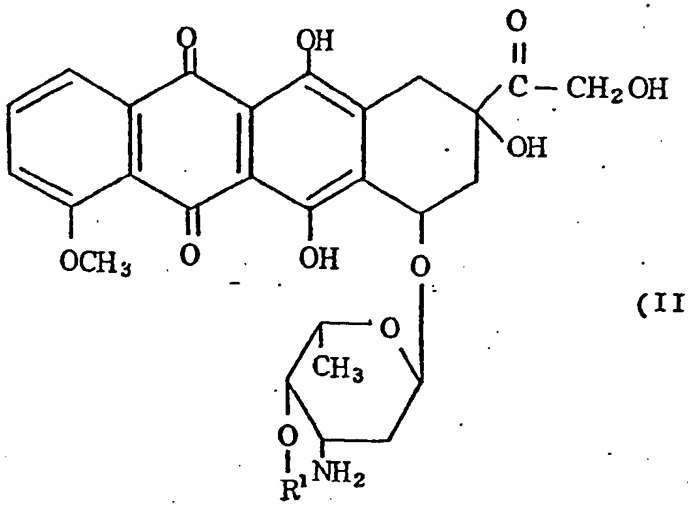
Compounds	No.			Yield	
4'-O-(tetrahydropyranyl)-ADM	1-a	-OH		16 %	See: Example 2
" (b)	1-b	"	"	21 %	
4'-O-(tetrahydrofuranyl)-ADM	2	-OH		46	
4'-O-(tetrahydrofuranyl)-ADM (a)	2-a	"	"		
" (b)	2-b	"	"		
4'-O-(6-acetoxymethyltetrahydropyranyl)-ADM	3	"		37	
4'-O-(1-ethoxyethyl)-ADM (a)	4-a	"		25	

				Yield
4'-O-(1-ethoxy-ethyl)-ADM (b)	4-b	-OH		24
4'-O-(1-butyloxy-ethyl)-ADM (a)	5-a	"		14
" (b)	5-b	"	"	17
4'-O-(1-iso-butyloxyethyl)-ADM (a)	6-a	"		18
" (b)	6-b	"	"	19
4'-O-(1-(6-methyl-heptyloxy)ethyl)-ADM (a)	7-a	"		15
" (b)	7-b	"	"	18
4'-O-(1-cyclo-hexyloxyethyl)-ADM (a)	8-a	"		16
" (b)	8-b	"	"	17

Claims

What we claim is:

(1) A method for preparation of anthracycline glycosides represented by formula (III) or their acid addition salts

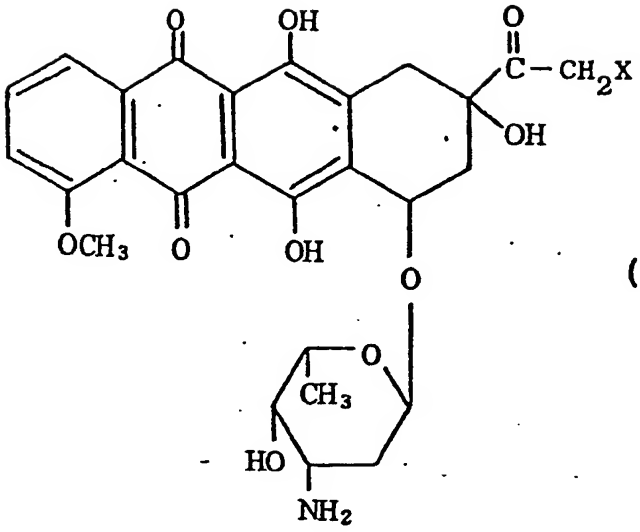


(III)

where R^1 is selected from the group consisting of hydrogen; tetrahydropyranyl; 6-substituted tetrahydropyranyl such as 6-acetoxymethyltetrahydropyranyl, 6-methoxytetrahydropyranyl and 6-carbomethoxytetrahydropyranyl; tetrahydrofuranyl; and alkyloxyethyl such as 1-methoxyethyl, 1-ethoxyethyl, 1-butyloxyethyl, 1-isobutyloxyethyl, 1-(6-methylheptyloxy)ethyl and cyclohexyloxyethyl,

in which

(a) 14-halogenodaunomycin represented by formula (I) or its salts that can be derived from daunomycin or its salts by halogenation in the presence of an inert organic solvent followed by acetone treatment;



(I)

where X is halogen atom,

(b) 14-halogenodaunomycin or its salts per se; or

(c) 14-halogenodaunomycin derivatives represented by formula (II) or their salts that can be obtained by treating 14-halogenodaunomycin or its salts in the presence of an acid catalyst in an organic solvent with dihydropyrane; dihydropyrane derivatives such as 2-acetoxymethyl-3, 4-dihydro-2H-pyrane, 2-methoxy-3,4-dihydro-2H-pyrane and 2-carbomethoxy-3,4-dihydro-2H-pyrane; dihydrofurane; and alkylvinyl ether such as methylvinyl ether, butylvinyl ether, isobutylvinyl ether, 6-methylheptyl-vinyl ether and cyclohexylvinyl ether;

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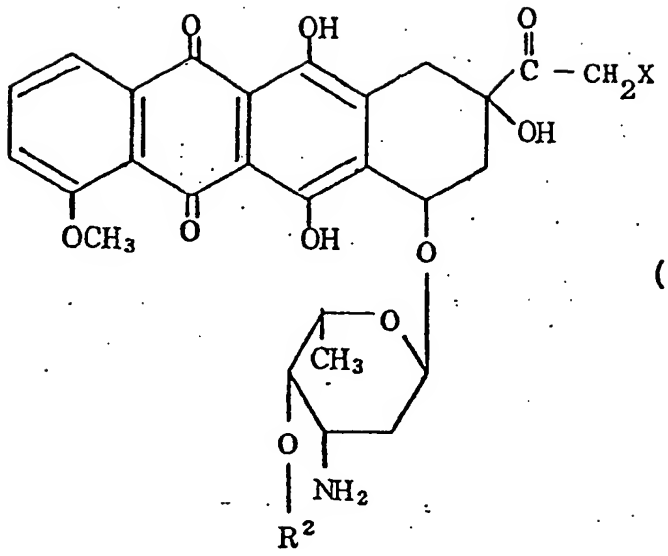

(II)

where R^2 is selected from the same group as defined for R^1 except hydrogen, X is the same as defined, are hydrolyzed by alkali treatment in a lower alcohol or aqueous acetone.

(2) The method for preparation of anthracycline glycosides or their acid addition salts as defined in claim 1, in which the starting material is 14-halogenodaunomycin represented by formula (I) which is derived from daunomycin or its salts by halogenation followed by acetone treatment.

(3) The method for preparation of anthracycline glycosides or their acid addition salts as defined in claim 1, in which 14-halogenodaunomycin or its salts per se are employed as the starting material.

(4) The method for preparation of anthracycline glycosides or their acid addition salts as defined in claim 1, in which the starting materials are 4'-substituted 14-halogeno-daunomycin derivatives or their salts that are obtained from 14-halogenodaunomycin or its salts by tetrahydro-pyranylation, 6-substituted-tetrahydropyranylation, tetrahydrofuranylation or alkyloxyethylation at position 4'.

European Patent Office

EUROPEAN SEARCH REPORT

0039060

Application number
EP 81 10 3104

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	US - A - 3 803 124 (F. ARCAMONE) * Column 10, lines 37-75; column 11,12 * --	1-4	C 07 H 15/24
	CHEMICAL ABSTRACTS, vol. 92, no. 17, April 28, 1980, page 629, abstract 147129g Columbus. Ohio, USA D. HORTON,"Adriamycin analogs hydroxylated at C-3': synthesis and antitumor activity" & Carbohydr. Res. 1979, 77, C 8-11 * Whole abstract * --	1-4	TECHNICAL FIELDS SEARCHED (Int. Cl.³) C 07 H 15/24
	GB - A - 2 002 754 (ZAIDANHOJIN) * Page 3 * --	1-4	
P	EP - A - 0 014 853 (ZAIDANHOJIN) * Pages 8-13 * --	1-4	
P	EP - A - 0 022 515 (C. ERBA) * Page 2, lines 24-28 * ----	1-4	

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L: citation for other reasons.

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	22-06-1981	VERHULST

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